UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/805,353	03/13/2001	Cayetano Gonzalez	9845-015	1937

20583 7590 08/17/2004

JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER
LEE, MATTHEW C

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 08/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/805,353	GONZALEZ ET AL.	
	Examiner	Art Unit	
	Matthew C Lee	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-133* is/are pending in the application.

4a) Of the above claim(s) *1-44,57-127, and 130-133* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-56, 128 and 129* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group III (claims 45-56, 128, and 129) in the reply filed on July 9, 2003 is acknowledged. The applicant asserts that Groups I-IX and XIV are neither independent nor distinct. The traversal is on the ground(s) that group I-III are all directed to computer implemented methods or to corresponding computer apparatus suitable only for practicing the method, and that the claims of group IV-IX and XIV all incorporate these computer methods and apparatus. This is not found persuasive because of the following reasons:

With regard to the distinctiveness of group I and II, the method of group I is directed to the rational engineering of macromolecules which includes nucleic acids, polysaccharides, fatty acids, and *inter alia*. The method of group II is directed to the rational engineering of polypeptides, which are materially different chemical species from other types of macromolecules. As stated in the examiner's previous action, group I and II are distinct from each other because they can be used to make materially different products, or the product can be made by other methods (MPEP §806.5(f)). For example, the method of group I can be used to engineer nucleic acids and polypeptides. In short, the basis for restricting groups I and II is as stated in MPEP § 806.5(f), not whether they are *in silico* or *in vivo* methods. Because examination of these two different methods would require non-coextensive search of non-patent literature, foreign patent, U.S. patent and U.S. publications, it is an undue burden of search and examination.

With regard to the applicant's argument of group I-III being similarly classified in class 700 and should be considered inseparable, the examiner also finds the argument not persuasive. The methods of group I and II, as recited, can be practiced using apparatus other than the computer system of group III. For example, the input molecular data can be represented by physical models made of properly calibrated magnetic properties, and the binding property estimated by appropriated measuring and computing. Therefore, the computer system of group III is patentably distinct from the methods of group I and II as recited.

With regard to the applicant's argument regarding groups IV-IX and XIV, directed to in vivo methods and apparatus, all have different classifications requiring divergent literature search and constitute an undue search burden. The applicant's argument is therefore not found to persuasive.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-44, 57-127, and 130-133 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions and species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 9, 2003.

IDS

The information disclosure statement filed on March13, 2001 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. It has been

placed in the application file, but the information referred to therein has not all been considered as to the merits. Non-considered references are missing at least one of the following: date of publication, source of publication, page number(s). It is noted that a listing of a URL, with no other identifying information, is not considered a proper citation on a PTO Form 1499. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Claim Rejections – 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49 and 50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for binding to one or two terminal sequences, does not reasonably provide enablement for binding to more than two terminal sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining what constitutes undue experimentation were affirmed by the court in *In re Wands* (8 USPQ2d 1400 (CAFC 1986)). These factors are the (1) quantity of experimentation; (2) the amount of direction or guidance presented in the specification; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the level of skill of those in the art; (7) predictability or unpredictability of the art; (8) and the breadth of the claims.

Claim 49 limits the system of claim 45 to one wherein estimation of binding is repeated until estimated binding of one or more candidates to two or more terminal peptide sequences of the selected target polypeptide is adequate. It is a common knowledge in the art that polypeptides are linear chains of amino acids and by definition can only have two termini. The specification does not disclose how to estimate binding to more than two termini. Although the level of skill in the art is high, because polypeptides with three termini is not known in the art, one of ordinary skill in the art would not know how to make use of the invention to engineering polypeptides that bind to "more than two" termini. The claim is therefore not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 45-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 45, 46 and 49, the terms "adequate" and “adequately” are relative terms which render the claims indefinite. The terms "adequate" and “adequately” are not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Because binding affinities is measured on a continuous scale and can take on any arbitrary values, merely stating “adequate” does not clearly defined the scope of the claim.

In claim 48, the term “consists essentially of” renders the claim indefinite because the number of amino acid residues to be considered as “terminal sequence” is not well defined (there is no consensus in the art as to the precise boundary of terminal sequences, nor is there clear definition in the disclosed written description), thereby rendering the scope of the claim unascertainable.

In claims 50, 52-55, the dependent claims refer to “The method…” of the parent claims whereas the subject of the parent claims is “The system of…” The meanings of the dependent claims are thus unclear.

Claim 51 is also rejected for the following reason:

Claim 51 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language. This claim is interpreted to be an omnibus type claim because

"Knowledge in the art" does not convey to a person of ordinary skill in the art the metes and bounds intended by the applicant.

Claim 46 is also rejected for the following reason:

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

In the present instance, claim 46 recites the broad recitation "less than approximately 20 residues", and the claim also recites "less than approximately 15, or 10, or 5 residues", which is the narrower statement of the range/limitation.

Claim Rejections – 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 45, 52, 53, 55 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nygen et al. (Curr. Opinion in Struct. Bio 1997, 7:463-469) in view of Patel et al. (IDS ref: J. of Computer-Aided Mol. Design, 1998, 12:543-536) and Dhiyat et al. (IDS ref: Science, 1997, 278:82-87).

Claim 45 is directed to a computer system implementing a method of designing peptides that bind to the terminal sequence(s) of a selected target protein wherein the design process comprises iteratively replacing side-chain residues and estimating the binding affinity of the resulting modified peptide, wherein the initial sequence of the peptide is selected from a set of peptides known to bind to the terminal sequence(s) of known target proteins. Claim 52 further limits the method of binding affinity estimation to CAMD methods for polypeptides. Claim 53 is dependent on claim 52 and further limits the CAMD methods to rotamer side-chain replacement and inverse-folding backbone determination. Claim 55 is dependent on claim 52 and further limits the CAMD method to comprise two more CAMD methods of increasing accuracy. Claim 56 is directed to a computer-readable medium encoding the program as recited in claim 45.

Nygen et al. teach the strategies of creating novel proteins/peptides capable of binding a desired target molecule by modifying a suitable protein domain that selectively binds terminal sequences of target ligands (pg. 463, column 2, last paragraph).

Nygen et al. does not teach computer implementation of the method.

Patel et al. teach the Computer-Aided Molecular Design (CAMD) techniques and systems used to design novel peptides wherein the design process comprises an iterative loop of modification/evaluation cycles (pg. 544, figures 1 & 2).

Dahiyat et al. teach the benefit of combining theory, computation and experiment in achieving faster speed in peptide design (pg. 86, column 3). They further teach an algorithm of automated peptide design that incorporates reverse-folding approach to design a peptide that fold to the desired 3D structure, which includes the use of rotamer side-chain replacement and other physical chemical potential functions (p82, column 2).

It would have been obvious to one of ordinary skill of the art at the time of invention to have computerized the method of Nygen et al. in the computer system as taught by Patel et al. and Dahiyat et al, where the motivation would have been to achieve faster speed and reduce experimentation in designing novel binding proteins/peptides, as taught by Dahiyat et al.

Claim 46 and 47 are also rejected under 35 U.S.C. § 103(a) as being unpatentable over Nygen et al. (Curr. Opinion in Struct. Bio 1997, 7:463-469), Patel et al. (IDS ref: J. of Computer-Aided Mol. Design, 1998, 12:543-536) and Dahiyat et al. (IDS ref: Science, 1997, 278:82-87) as applied in claims 45, 52, 53 and 56 above, and in further view of Schneider et al. (IDS ref: Nature biotech 1999, 17:170-175). Claim 46 limits peptides to be less than 20, 15, 10, or 5 residues. Claim 47 further limits the scope of claim 45 wherein the data representing the terminal sequences of the selected target used for design comprises either N-terminus or C-terminus or both termini of the selected target.

Nygen, Patel and Dahiyat make obvious a computer system and method for engineering peptides which bind to terminal peptide sequences, as set forth above.

None of Nygen, Patel or Dahiyat specifically teach using N-termal or C-terminal sequences or both as representing the selected target in the said computer system.

Schneider et al. teach that engineered PDZ domains can recognize C-terminal peptide sequences of different targets and can be used as a precursor polypeptide for artificial modification to bind desired target sequences (pg 170, abstract). Schneider et al. further teach an example of binding target consisting of 9 amino acid residues, which after the engineered PDZ was able to bind with a k_d raninging from nM to μM (pg. 171 column 2, bottom 4 lines).

It would have been obvious to one of ordinary skill of the art at the time of the invention to limit the data representing the selected targets in the computer system of Nygen, Patel and Dahiyat to at least C-terminal sequences, where the motivation would have been to utilize PDZ domains as precursor peptides as taught by Schneider et al.

Claim 48 is also rejected under 35 U.S.C. § 103(a) as being unpatentable over Nygen, Patel and Dahiyat, as applied in claim 45, 52, 53, 55, and 56 in further view of Bohm (IDS ref: J. of Computer-Aided Mol. Design, 1998, 12:309-323). Claim 48 further limits the data representing the precursor polypeptide in the computer system of claim 45 to comprise 3D structures and limits the data representing the selected target peptide to consist essentially of one or more of its terminal sequences.

Nygen, Patel and Dahiyat make obvious the computer system of claim 45, wherein protein design comprises CAMD.

None of Nygen, Patel and Dahiyat teach the limitation of precursor poplypeptide comprising 3D structures.

Bohm teaches a fast method of predicting the binding constants of protein ligands requiring 3D structural information.

It would have been obvious to one of ordinary skill in the art at the time of the invention to include 3D structural information, as taught by Bohm in the system and method of Nygen, Patel and Dahiyat, where the motivation would have been to increase the accuracy of prediction by including geometrical analysis as taught by Bohm (pg 321, left column).

Claim 49, 50 and 128 are also rejected under 35 U.S.C. § 103(a) as being unpatentable over Nygen, Patel and Dahiyat in further view of Terskikh et al. (PNAS 1997 94:1663-1668). Claim 49 further limit the computer system of claim 45 to wherein the precursor polypeptide binds to two or more terminal peptide sequences of the initial target peptide. Claim 50 further limits the computer system of claim 49 wherein the terminal peptide sequences of the selected target comprise both the N-terminal and the C-terminal peptide sequence whereby the candidate poplypeptide are engineered to bind bivalently to the selected target polypeptide.

Nygen, Patel and Dahiyat make obvious the computer system of claim 45, wherein the engineered candidate polypeptides bind to one or more terminal sequences of target polypeptide.

Nygen and Patel do not teach the use of multivalent binding in the computer system of Nygen, Patel and Dahiyat.

Terskikh et al. (PNAS, 1997, 94:1663-1668) teach the creation of multi-functional short peptide ligands that bivalently bind to a target can increase binding affinity by as much as 2 X 10^5 fold (p1663, abstract). It would have been obvious to one of ordinary skill in the art at the time of the invention to use bivalency as a design criteria where the motivation would have been to achieve higher specific binding affinities in the designed binding polypeptides.

Claim 51 is also rejected under 35 U.S.C. § 103(a) as being unpatentable over Nygen, Patel and Dahiyat as applied to claim 45 in further view of Eldridge et al. (IDS ref: J. Computer-Aided Molecular Design, 1997, 425-445). Claim 51 further limit the computer system of claim 45 wherein the method of rational binding-estimating comprises a priori chemical or physical principle based, or empirical rules based, or knowledge in the art.

Nygen, Patel and Dahiyat make obvious the computer system of claim 45, wherein the engineered candidate polypeptides bind to one or more terminal sequences of target polypeptide.

None of Nygen, Patel and Dahiyat teach the method of rational binding-estimating as comprised of a priori chemical or physical principle based, or empirical base, or knowledge in the art.

Eldridge et al. teach an overview of physical/chemical and empirical methods of estimating binding affinity commonly known in the art. It would have been obvious for one of ordinary skill in the art to use any methods described by Eldridge et al. to estimate binding energy in a computer system that rely on this value to design binding peptides,

where the motivation would have been to find and use lowest energy binding parameters, as taught by Dahiyat (p84).

Claim 54 is also rejected under 35 U.S.C. § 103(a) as being unpatentable over Nygen, Patel and Dahiyat as applied in claim 45 in further view of Lacroix et al. (U.S. 2002/0072864 filed on 8/3/1999). Claim 54 further limits the CAMD methods to a Perla method.

Nygen, Patel and Dahiyat make obvious the computer system of claim45, wherein protein design comprises CAMD methods.

Nygen, Patel and Dahiyat do not teach Perla.

Lacroix teaches Perla which is a CAMD method that searches in protein sequence space to uncover optimal amino acid sequences for desired protein 3D structure.

It would have been obvious to a person of ordinary skill in the art to incorporate Perla as a CAMD method in the protein engineering system of Nygen, Patel and Dahiyat where the motivation would have been to reliably model small changes in protein structure as taught by Lacroix (pa. 8).

Claim 128 and 129 are also rejected under 35 U.S.C. § 103(a) as being unpatentable over Nygen, Patel, Dahiyat and Bohm.

Claim 128 is directed to a computer system for engineering binding polypeptides comprising of data and computer program wherein the data are limited to (i) data representing selected target polypeptide consisting of terminal sequences less than

approximately 15 residues. (ii) data representing the precursor polypeptide comprises sequence, 3D structure, and terminal sequences of the initial target with length less than approximately 15 residues. And the program instructions are limited to: (i) rational engineering methods to replace the side-chains of candidate polypeptide for stronger binding (ii) rational binding-estimating methods comprising one or more CAMD methods, and (iii) repeat side-chain replacement and binding estimation until estimated k_d is less than 100 μM.

Claim 129 further limits the length of polypeptide to less than approximately 10 residues.

Nygen, Patel, Dahiyat and Schneider make obvious a computer system and method of engineering peptides which bind to terminal sequences, specifically C-term sequences comprising 9 residues and various K_d values, as set forth above.

Bohm teaches a fast method of predicting the binding constants of protein ligands requiring 3D structural information.

None of Nygen, Patel, Dahiyat or Schneider teach limiting the data representing precursor peptides to 3D structures.

It would have been obvious to one of ordinary skill in the art at the time of the invention to include 3D structural information, as taught by Bohm in the system and method of Nygen, Patel, Dahiyat, and Schneider where the motivation would have been to increase the accuracy of prediction by including geometrical analysis as taught by Bohm (pg 321, left column).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Matthew C Lee whose telephone number is (571) 272-2931. The examiner can normally be reached on 8am - 4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MICHAEL P WOODWARD can be reached on (571) 272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Matthew C. Lee
Examiner, Art Unit 1631
08/13/2004

MARJORIE MORAN
PATENT EXAMINER
Marjorie A. Moran
8/13/04